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A predictive model for survival of gallbladder adenocarcinoma

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ABSTRACT

Background: Gallbladder cancer (GBC) is a life-threatening disease with a poor prognosis worldwide. Although several risk factors for survival have been identified, an ideal model for predicting prognosis has still not been developed due to the low incidence of GBC. This study aims to solve this dilemma by attempting to develop an efficient survival prediction model for GBC.

Methods: This is a retrospective study. From January 2009 to June 2016, 164 patients with a confirmed histological diagnosis of gallbladder adenocarcinoma were enrolled in this study. The cohort was randomly divided into two cohorts, the development cohort (n = 110) and validation cohort (n = 54). On the basis of the risk factors identified in the development cohort, a nomogram-based predictive model (P-risk Plus), composed of carbohydrate antigen 199 and pathological characteristics, was established for prognosis.

Results: In this model, the calibration curves for the 1-, 2-, and 3-year survival probabilities were well-matched with the actual survival rates. In addition, the highest C-index and best decision curve analysis were able to be obviously determined. Meanwhile, the P-risk Plus model result yielded a better fit for survival between the development and validation groups.

Conclusion: Compared with conventional tumor stages, our nomogram-based P-risk Plus model for gallbladder adenocarcinoma has a better predictive capacity and thereby has a better potential to facilitate decision-making clinically.

1. Introduction

Gallbladder cancer (GBC) is an uncommon, but one of the most life-threatening, neoplasms worldwide, and GBC is most frequently identified as adenocarcinoma by pathologists [1]. At present, surgical resection is the only curative therapeutic approach and has a 5-year overall survival rate for later stage patients of less than 10% [2–4]. Unfortunately, most patients are diagnosed at advanced stages of GBC because this malignancy always progresses asymptomatically. Given the low incidence of GBC, the curative effect of adjuvant treatment (AT), including chemotherapy, radiotherapy and concurrent chemo-radiotherapy, is still controversial [5–7]. Even though adjuvant chemotherapy is recommended for high-risk patients (e.g., lymph node positive, microscopic positive margins, etc.), the evidence that supports the benefits of postoperative AT remains scarce [8].

Over recent decades, many efforts have been made to explore prognostic factors, such as the histological type, lymph node invasion, tumor stage, and so on. The traditional tumor stages, namely, the tumor–node–metastasis (TNM) staging from the American Joint Committee on Cancer (AJCC) and Nevin staging, have been the most valuable predictors of GBC prognosis [9]. However, these predictive models only focus on pathological outcomes and ignore demographic characteristics, which could have a large effect on prognosis [10–12]. Therefore, establishing a comprehensive model that goes beyond the pathological features of GBC for predicting prognosis is necessary. With the ability to generate an individual probability of a clinical event by integrating diverse prognostic and determinant variables, a nomogram-based predictive model for GBC has long been of interest. With the use of a user-friendly digital interface, such a nomogram-derived prognostic model is easily understood and has a better predictive capability compared with conventional staging.

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Therefore, the aim of this study is to develop a nomogram-based predictive model for determining the prognosis of gallbladder adenocarcinoma. By improving the predictive capacities of gallbladder adenocarcinoma, our model has the potential to aid in decision making in clinical settings.

2. Methods and materials

2.1. Patients and methods

From our clinical database, patients with a confirmed histological diagnosis of gallbladder adenocarcinoma were eligible in this study. This study was approved by the Ethical Committees for Human Subjects at Sir Run Run Shaw Hospital, affiliated with Zhejiang University, China. For patient selection, the inclusion criteria were as follows: 1) histologically proven gallbladder adenocarcinoma; 2) ASA $\leq$ III and eastern cooperative oncology group score $\leq$1; 3) no signs of distant metastasis; and 4) no neoadjuvant treatments before surgery that could lead to bias in the retrospective study. From January 2009 to June 2016, 164 consecutive patents were enrolled.

After a detailed history and complete physical examination, biochemistry tests, tumor markers, and imaging examinations were performed. With respect to the surgical strategy, a simple cholecystectomy was performed for patients with Tis or T1a tumors according to the TNM stage (7th edition [13]). For T1b GBC tumors and above, an extended cholecystectomy involving resection of the gallbladder, partial hepatectomy (gallbladder bed), dissection of regional lymph nodes, and resection of adjacent organs if invaded was the standard treatment [14]. After hospital discharge, patients were regularly followed up every three to six months until the fifth year.

The clinicopathological characteristics, including age, gender, body mass index (BMI), serum carbohydrate antigen 199 (CA199), carcinoembryonic antigen (CEA), Child-Pugh score, tumor size, adjacent organ invasion, lymph node invasion, perineural invasion, differentiation, surgical margins, tumor stage and postoperative adjuvant chemotherapy or radiotherapy, were collected retrospectively. As only a few patients underwent simple cholecystectomy, the type of surgery was not included in this study. The primary end points were disease-free survival (DFS) and overall survival (OS), which were defined as the time from surgery to recurrence and death or last follow-up, respectively. The survival rate was equal to 1- No. of recurrences or deaths/(No. of patients at risk + No. of recurrences or deaths + No. censored/2) *100%. The number of patients evaluated is summarized in Supplement Figure 1.

2.2. Statistical analysis

Initially, the entire cohort was randomly divided into two cohorts: the development cohort (n = 110) and validation cohort (n = 54). To establish the P-risk Plus model, calibration was performed by bootstraps with 500 resamples using R software (version 3.3.3) with the "*rms*" package. The concordance index (C-index) and decision curve analysis (DCA) were used to evaluate the predictive capacity.

The continuous variables and categorical data are expressed as the median, including the range, and number, including the proportion, respectively. Survival curves were drawn using the Kaplan-Meier method. Statistical tests were two sided, and P values less than 0.05 indicated a significant difference. Calculations were performed using SPSS, version 22.0 for Windows (IBM Corporation, Armonk, NY).

3. Results

3.1. Clinicopathological characteristics

A total of 164 patients were enrolled, and no patient in this study died of non-cancerous causes. Overall, the postoperative 1-, 2-, and 3-year DFS and OS rates were 86.9%, 77.8%, and 63.9% and 75.7%, 63.8%, and 58.7%, respectively (Supplement Figure 1). After randomization, 110 patients were assigned to the development cohort, while 54 patients were assigned to the validation cohort. The median follow-up in the development and validation cohorts was 25.5 months (range, 3–98 months) and 23.5 (range, 3–80 months), respectively. The demographic characteristics,

Table 1
Clinicopathological characteristics.

	Development cohort (n = 110)	Validation cohort (n = 54)
Age,years	62.0 (39–85)	60.0 (42–81)
Gender		
Male	25 (22.7%)	15 (27.8%)
Female	85 (77.3%)	39 (72.2%)
BMI, kg/m^2	23.2 (17.3–32.9)	23.6 (14.6–31.4)
CA199, IU/mL	13.6 (0.1–1000.0)	18.7 (1.1–1000)
CEA, ng/mL	1.9 (0.4–300.0)	2.6 (0.8–273.0)
Child-Pugh grade		
A	104 (94.5%)	50 (92.6%)
B	6 (5.5%)	4 (7.4%)
Tumor size, cm	2.6 (0.4–8.0)	3.0 (0.3–9.0)
Adjacent organs invasion		
Absent	90 (81.8%)	42 (77.8%)
Present	20 (18.2%)	12 (22.2%)
Lymph node invasion		
Negative	79 (71.8%)	36 (66.7%)
Positive	31 (28.2%)	18 (33.3%)
Perineural invasion		
Absent	92 (83.6%)	45 (83.3%)
Present	18 (16.4%)	9 (16.7%)
Differentiation		
Well	40 (36.4%)	17 (31.5%)
Moderate	43 (39.1%)	12 (22.2%)
Poor	27 (24.5%)	25 (46.3%)
Margin		
Negative	104 (94.5%)	51 (94.4%)
Positive	6 (5.5%)	3 (5.6%)
TNM stage		
0	2 (1.8%)	1 (1.9%)
I	14 (12.7%)	3 (5.6%)
II	51 (46.4%)	27 (50.0%)
III	43 (39.1%)	23 (42.6%)
IV	0 (0%)	0 (0%)
Nevin stage		
I	2 (1.8%)	1 (1.9%)
II	14 (12.7%)	3 (5.6%)
III	51 (46.4%)	27 (50.0%)
IV	23 (20.9%)	11 (20.4%)
V	20 (18.2%)	12 (22.2%)
Postoperative adjuvant chemotherapy		
Absent	94 (85.5%)	46 (85.2%)
Present	16 (14.5%)	8 (14.8%)
Postoperative adjuvant radiotherapy		
Absent	92 (83.6%)	39 (72.2%)
Present	18 (16.4%)	15 (27.8%)

Data are presented as number with percentage and median with range. BMI, body mass index; CA199, carbohydrate antigen; CEA, carcinoembryonic antigen; Adjacent organs invasion include stomach, duodenum, pancreas, kidney, colon, etc. TNM stage is according to the AJCC 7th edition.